REMARKS

By the present communication, claim 20 is amended. No new matter is introduced by the amendment as the amended and new claim language is supported by the application as originally filed, including but not limited to, paragraphs 14 and 45. A complete listing of the claims as currently pending, with appropriate status identifiers included, is found on pages 3-13 of this document. Thus, after entry of the claim amendments, claims 1-38 and 49-64 will be pending in the application.

Applicants respectfully request reconsideration of the present application in view of the foregoing amendment and in view of the reasons that follow.

I. Claim Objections

Claim 51 is objected to under 37 C.F.R. § 1.75(c) as allegedly being of improper dependent form for not further limiting the subject matter of claims 49 and 50 from which claim 51 depends (directly and indirectly, respectively). Because claim 51 does, in fact, differ in scope from claims 49 and 50, Applicants respectfully traverse this rejection.

Claim 51 properly depends from and is entirely consistent with claims 50 and 49. Claim 51 defines the duration and dosing protocol for a single treatment cycle. Thus, claim 51 recites that the treatment cycle comprises administering the same amount of compound daily for 7 days followed by 7 days without administration of the compound. By comparison, claims 49 and 50 define how the amount of compound administered varies between treatment cycles. Claim 49, for example, recites that the amount of compound administered to a subject in a first treatment cycle is 25 mg per day, and the amount increases with subsequent treatment cycles. Claim 50 further specifies that the amount of compound administered is doubled with each subsequent treatment cycle. Therefore, the treatment cycle of claim 51 in which the same amount of compound is administered daily for 7 days as part of a 14 day cycle is consistent with claim 50, calling for doubling the amount of compound administered with each subsequent treatment cycle. Accordingly, Applicants respectfully request the withdrawal of the present objection.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

A. Written Description

Claims 1-38, and 49-64 stand rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The Examiner alleges that the recitation in claims 1, 9, 49, 52 and 53 that the cancer being treated "comprises cells expressing a receptor tyrosine kinase," is new matter. It is asserted that "there is no disclosure in the claims and specification as originally filed that applicants only intended to treat only cancers wherein the cancer cells express a receptor tyrosine kinase." Office Action, p. 4. Applicants respectfully remind the Examiner that there is no *in haec verba* requirement with regard to support for claim amendments and traverse this rejection for the reasons that follow.

Applicants previously pointed to paragraphs 81 and 82 as support for the amended language of claims 1, 9, 49, 52, and 53. The Examiner alleges that these paragraphs are directed to effective amounts of the claimed compounds and do not teach that the Applicants intend to treat cancer cells that express receptor tyrosine kinase (abbreviated RTK as disclosed in paragraph 5 of the application). While paragraph 81 does disclose effective amounts of compounds that inhibit RTKs involved in cancer, paragraph 82 contains additional support for the rejected language. Paragraph 82 is reprinted below:

> **[0082]** An RTK disorder, or RTK-mediated disease, which may be treated by those methods provided, include any biological disorder or disease in which an RTK is implicated, or which inhibition of and RTK potentiates a biochemical pathway that is defective in the disorder or disease state. Examples of such diseases are cancers such as prostate, colorectal, breast, multiple myeloma, pancreatic, small cell carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, or myelo-proliferative disease.

This paragraph clearly states that "an RTK disorder, or RTK-mediated disease,...may be treated by those methods provided," and includes any biological disorder or disease in "which

inhibition of an RTK potentiates a biochemical pathway that is defective in the disorder or disease state." The paragraph further identifies a number of cancers that are mediated by RTKs. That this disclosure contemplates the treatment of cancer comprising cells expressing an RTK is further supported throughout the application. The application additionally teaches that RTKs such as VEGF-RTK, FGF-RTK, and PDGF-RTK play active roles in angiogenesis and cancer (paragraphs 4-9), and that the compound of formula I and other compounds disclosed therein inhibit RTKs involved in angiogenesis and cancer (paragraphs 10, 11, 47, and 81), and provides data showing the inhibition of RTKs (Examples 3 and 10) and the inhibition of cancer and angiogenesis (Examples 1, 4, 5, and 8). It is therefore clear that Applicants intended to treat cancers which express RTKs and may therefore claim such treatment.

Accordingly, the application, including paragraphs 81 and 82, provides the requisite disclosure for the amended language, and that language does not constitute new matter. Applicants respectfully request that the Examiner remove this ground of rejection.

B. Enablement

Claims 1-24, 28-38, and 49-64 are rejected under 35 U.S.C. § 112, first paragraph, because, allegedly, the specification while "enabling for the treatment of KM1214a in mice...does not reasonably provide enablement for the treatment of any and all cancers with amounts of the claimed compound 'to provide' the claimed C_{max}..., plasma concentrations, and AUC." Office Action, page 5, emphasis added. In the Office Action it is also alleged that because the "instant claims do not recite the measurement of a C_{max},...it is unclear how one skilled in the art would know when an appropriate dosage is being administered." *Id.* Finally, the Examiner asserts that the "claims, nor the specification recite any particular dosages, routes of administration, frequency of administration, etc. necessary to treat any and all cancers." *Id.* Applicants respectfully disagree with each stated reason and traverse this rejection.

The Treatment of Cancer Cells Expressing A Receptor Tyrosine Kinase.

Contrary to the assertion in the Office Action that treatment of all cancers is encompassed by the claims, Applicants point out that the claims recite, in part, "[a] method for treating cancer, wherein the cancer comprises cells expressing a receptor tyrosine kinase..." (emphasis added). Thus, it is plainly clear that Applicants have *not claimed* the treatment of *any and all* cancers, but rather the treatment of *only* those cancers expressing a receptor tyrosine kinase.

The specification exemplifies the inhibitory effects of the claimed compounds against the very types of cancers recited in the claims: those mediated by RTKs. As illustrated by Example 1, the claimed compounds are effective in inhibiting proliferation of a large number of cancer cell lines, the proliferation of which is dependent upon one or more RTKs. The cancer cells lines that are inhibited by the claimed compounds include MV4; 11 (AML, acute myelogenous leukemia), KM12L4a (colon cancer), HMVEC (VEGF/VEGF R2 mediated; endothelium), TF-1 (SCF/c-KIT mediated; AML), RS4 (ALL, acute lymphoid leukemia), 4T1 (mouse breast cancer), MDA-MB435 (breast cancer), SKOV3 (ovarian cancer), K562 (CML, chronic myelogenous leukemia), Ku812 (CML), MOLT-4 (ALL), ARH77 (multiple myeloma), HCT116 (colon cancer), Du145 (prostate cancer), PC3 (prostate cancer), H209 (lung cancer), H226 (lung cancer), HT29 (colon cancer), SW620 (colon cancer), PrC (normal prostate epithelium), and HMEC (normal mammary epithelium). Table 1 provides EC_{50} data for each of these cell lines, showing the measured inhibitory effects of compound 1 on cancer cell lines dependent upon RTKs for proliferation.

Applicants also point to Example 3, where it is shown that the claimed compound exhibits potent inhibitory effects on a number of individual RTKs (paragraphs 91-96). The Example illustrates IC_{50} values for VEGFR1 (FLT-1), VEGFR2 (FLK1), bFGFR, PDGFR, Flt3, and c-kit in the presence of the claimed compounds. Thus, the application provides specific data showing that the claimed compounds inhibit RTKs known to be expressed by numerous types of cancer cells.

In addition to the inhibition of KM12L4a tumors in mice as shown in Example 4, Applicants also direct the Examiner's attention to Example 5, where PC3 human prostate cancer cells were implanted into tumor model mice (paragraph 110). Example 5 illustrates "significant...tumor inhibition in all treatment groups" (paragraph 112). The results, presented in Tables 4 and 7, clearly show the effectiveness of the compound against such cancers. Thus, *in-vivo* cancer treatments in addition to the KM12L4a tumors have been exemplified.

Example 8 illustrates the effectiveness of the claimed compounds at inhibiting angiogenesis as assessed by the growth of Matrigel plugs supplemented with 2 μg FGF-2. FGF-2 supplements blood vessel formation in Matrigel plugs when untreated. Table 8 then illustrates the percent inhibition versus administration of vehicle without any active agents. In some examples, the percent inhibition using the claimed compounds was in excess of 90%.

As confirmation of the effectiveness of the claimed compounds at inhibiting RTKs and cancer, Applicants draw the Examiner's attention to the fact that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, the compound found in independent claims 1, 9, 36, and 49, and also one of the compounds in independent claims 52 and 53, is currently undergoing separate Phase II clinical trials for multiple myeloma (MM) and acute myelogenous leukemia (AML). The clinical trials were based in part on data in the present application and in three references, submitted herewith. The appended references show tumor regression and *in-vivo* target modulation of receptor tyrosine kinases in colon cancer, MM, and AML cells. Particularly, in MV4;11 tumors (AML tumor cells having FLT3 mutations), target modulation of pFLT3, pSTAT5 and pERK was achieved with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, and tumor regressions and eradication of AML cells from bone marrow were shown in s.c. and bone marrow engraftment leukemic xenograft models. *Clin Cancer Res* 2005;11 (14) p.5281-91. In a separate colon cancer study, immunohistochemical analysis showed reduction of phosphorylated PDGFB and pERK in tumor cells after oral dosing with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, accompanied by a decreased tumor cell proliferation rate

and reduced intratumoral microvessel density. *Clin Cancer Research* 2005;11 (10) p.3633-41. Finally, in primary myeloma cells from patients having the t(4;14) IgH translocation, 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibited downstream extracellular signal-regulated kinase phosphorylation and further displayed therapeutic efficacy in a xenograft mouse model of FGR3 MM. *Blood* 2005:105 p.2941-48.

It is readily apparent that Applicants have provided not only a plethora of data related to the inhibition of RTKs, and RTK dependent cancer cells, using the claimed compounds, but Applicants have also shown that the compounds are effective in treating cancers, in which the cancer cells express RTK, in Phase I clinical trials. Such extraordinary depth of data illustrates and supports the claimed methods of "treating cancer, wherein the cancer comprises cells expressing a receptor tyrosine kinase..." Contrary to the Examiner's assertion, Applicants have not claimed the treatment of any and all cancers, but rather only those cancers that comprise cells expressing a receptor tyrosine kinase, as is consonant with the teachings of the specification and the large number of examples related to RTK inhibition.

Measurement Is Not An Essential Step.

The Examiner also alleges that the claims are missing an essential step. Specifically, the Examiner states that the claims do not recite the measurement of a C_{max}, plasma drug concentration, or AUC (Office Action, page 5), and that such a step is essential to guide one of skill in the art. Applicants submit that such a step is not essential.

Measurement of a C_{max}, plasma drug concentration, or AUC is not essential to practice the present methods because, e.g., Applicants have provided dosages that will provide the claimed blood and plasma levels. Paragraphs 17, 46, and 58 of the specification describe that "the amount of the compound of formula I administered to the subject ranges from 0.25 to 30 mg/kg body weight of the subject," and that "the amount of the compound administered to the subject ranges from about 25 to 1500 mg/day," As shown in Table 5 of the specification, administration of the compound to mice in amounts ranging from 3 to 30 mg/kg/day, provides

the claimed ranges of the drug concentration, C_{max}, and AUC in blood and plasma. Thus, one of skill in the art will readily observe that with the guidance of the instant specification in hand, administration of the compound at the provided body weight dosages will result in the claimed plasma and blood levels without a need to separately measure those levels for each and every subject to which the compound is administered.

Indeed, clinicians do not routinely test blood and plasma levels for a particular pharmaceutical agent in blood or plasma, but rather they typically rely on the information provided by other providers (i.e. a pharmaceutical company) to indicate what dosage levels will produce the desired blood and plasma levels. Here, the Applicants have provided one of ordinary skill in the art, e.g., the clinician, with the guidance to establish the claimed blood and plasma levels of the compound(s) in a subject. To the extent that any experimentation is necessary to provide the stated blood levels, Applicants submit that it is routine in the art. The clinician need not separately determine those levels for each and every subject upon which the method is practiced.

Dosages, Routes of Administration, and Frequency.

In the Office Action it is further alleged that the specification does not recite any particular dosages, routes of administration, frequency of administration, etc. to treat any and all cancers. As above, Applicants point out that it is not necessary to support the treatment of any and all cancers, only those cancers that are claimed. The only cancers claimed are those that express RTK. Contrary to the Examiner's assertion, the specification does recite dosages, routes, and frequencies of administration to guide the skilled artisan in achieving the claimed blood and plasma levels of the recited compounds.

As discussed above, Applicants have provided dosages that will provide the claimed blood and plasma levels. Paragraphs 17, 46, and 58 of the specification describe that "the amount of the compound of formula I administered to the subject ranges from 0.25 to 30 mg/kg body weight of the subject," and that "the amount of the compound administered to the subject

ranges from about 25 to 1500 mg/day," As shown in Table 5 of the specification, administration of the compound to mice in amounts ranging from 3 to 30 mg/kg/day, provides the claimed ranges of the drug concentration, C_{max}, and AUC in blood and plasma. Thus, one of skill in the art will readily observe that with the guidance of the instant specification in hand, administration of the compound at the provided body weight dosages will result in the claimed plasma and blood levels without a need to separately measure those levels for each and every subject to which the compound was administered.

With further regard to dosages, Applicants point to paragraph 80 where it is stated that "[s]pecific dosages may be adjusted depending on conditions of disease, the age, body weight, general health conditions, sex, diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs." Applicants also point to paragraph 46 where the dosage is recited as mg of the compound per kg of body weight of the subject. It is not an object of the present invention to describe the exact dosage for every single subject that may be administered or exposed to the compound(s). The inventors leave that to a subject's clinician to decide based upon disease, the age, body weight, general health conditions, sex, diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs, but with the guidance provided by the claims and/or the amount of the compound based upon the body weight of the subject.

The application also describe the dosage forms that may be prepared (paragraphs 68-79). These include routes of oral, intranasal, transmucosal, rectal, subcutaneous, intrathecal, intravenous, intramuscular, intraperitoneal, intraocular, or intraventricular. The forms include, but are not limited to granules, powders, tablets, capsules, syrups, suppositories, injections, emulsions, elixirs, suspensions, and solutions.

Paragraph 48 describes the frequency of administration:

> For example, the treatment cycle may comprise administering the amount of the compound of formula I daily for 7, 14, 21, or 28 days, followed by 7 or 14 days without administration of the

> compound. In some embodiments, the treatment cycle comprises administering the amount of the compound daily for 7 days, followed by 7 days without administration of the compound. A treatment cycle may be repeated one or more times to provide a course of treatment. In addition, the compound may be administered once, twice, three times, or four times daily during the administration phase of the treatment cycle. In other embodiments, the methods further comprise administering the amount of the compound once, twice, three times, or four times daily or every other day during a course of treatment.

Based upon the above described disclosure of dosages, routes of administration, frequency of administration, and more, Applicants respectfully submit that there is simply no basis to assert a lack of such description and guidance in the application. Applicants respectfully request that the Examiner withdraw the rejection of claims 1-24, 28-38, and 49-64 under 35 U.S.C. § 112, first paragraph for lack of enablement.

III. Rejections Under 112, Second Paragraph

A. Claim 20

Claim 20 is rejected under 35 U.S.C. § 112, second paragraph as being indefinite for the use of the phrase "the solid compound," because the term "solid" lacks antecedent basis. Applicants respectfully submit that this rejection is moot in view of the amendment to claim 20.

B. Claims 1-38, 52-61, and 63-64.

Claims 1-38, 52-61, and 63-64 stand rejected under 35 U.S.C. § 112, second paragraph as being incomplete for omitting essential steps. The Examiner alleges that a step of measuring the C_{max}, AUC, or plasma concentration following administration of the compound is essential to the claims. Applicants direct the Examiner's attention to the remarks in section II, above, in traversing this rejection. In view of those remarks, Applicants submit that the grounds for this rejection are overcome.

IV. Double Patenting

A. U.S.S.N. 10/116,117

Claims 1-7, 9-12, 14, 25-30, 36-38, and 52-64 stand provisionally rejected on the grounds of obviousness-type double patenting (ODP) over claims 38, 40, and 49-52 in copending U.S.S.N. 10/116,117 (the '117 application). Applicants respectfully traverse this rejection.

The standard for the analysis employed in an ODP determination parallels that of a 35 U.S.C. § 103(a) rejection (M.P.E.P. 804(II)(B)(1)). To establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), it must be shown that there is

> some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally the prior art reference...must teach or suggest all the claim limitations.

(see M.P.E.P. § 2143.)

Applicants also point out that according to M.P.E.P. § 804(III), a

> significant difference [between an ODP rejection and an anticipation rejection] is that a double patenting rejection must rely on a comparison with the claims in an issued or to be issued patent, whereas an anticipation or obviousness rejection...relies on a comparison with what is disclosed in the same issued or to be issued patent.

(Emphasis added). As set forth in M.P.E.P. § 804(III), it is the claims of the issued patent that must be the basis for an ODP rejection. Applicants submit that based upon this requirement, a *prima facie* case of obviousness has not been established on several grounds: first there is no suggestion or motivation in any of claims 38, 40, or 49-52 of the '117 application to modify the claims to recite the currently claimed ranges and/or metabolites, second, there is no reasonable

expectation of success in doing so, and finally all the claim limitations are not taught or suggested.

The rejected claims include the following subject matter. Independent claim 1, from which claims 2-7 and 59 depend, recites administering a sufficient amount of a compound (or salts or tautomers thereof) to provide a given range of C_{max} of the compound in the subject's plasma or a given range of C_{max} of the compound in the subject's blood. Independent claim 9, from which claims 10-12, 14, 25-30, and 60 depend, recites administering a sufficient amount of a compound (or salts or tautomers thereof) to provide a given range of the compound in the subject's plasma or a given range of the compound in the subject's blood 24 hours after administration. Claims 25-27 further specify the amount of the compound administered based upon the body weight of the subject. Independent claim 36, from which claims 37, 38, and 61 depend, recites administering a sufficient amount of a compound (or salts or tautomers thereof) to provide a given range of AUC of the compound in the subject's plasma or a given range of AUC of the compound in the subject's blood.

There is No Teaching or Suggestion of Each Claim Element.

Claims 38, 40, and 49-51 of the '117 application are, in general, directed to methods of treating cancer cells expressing a receptor tyrosine kinase by administering 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one either alone, in combination with isomer or salt analogs, or in combination with other anti-cancer treatments. Claim 38 is directed to the administration of the compound. Claim 40 is directed to the administration of the compound in combination with an anti-cancer drug. Claims 49-51 specifically recite particular RTKs.

There simply is no suggestion or teaching in these claims of the presently claimed concentrations, or C_{max} or AUC levels of the compounds in a subject's plasma or blood. Without some such teaching or suggestion the third prong (i.e. a teaching or suggestion of all of the claim limitations) of the establishment of a *prima facie* case of obviousness must fail.

There is No Motivation to Select.

Assuming *arguendo,* the cited claims of the '117 application encompass doses that would provide the claimed ranges or values, Applicants traverse the rejection on grounds that there is no teaching or suggestion to select the claimed ranges or values. According to M.P.E.P. § 2144.08(II)(A)(4)(a), in establishing a *prima facie* case of obviousness, the size of the genus must be considered, stating that "some motivation to select the claimed species or subgenus must be taught by the prior art." Emphasis added. Further, according to M.P.E.P. 2144.05(I), "if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus." This is exactly the situation at hand in the instant application.

The Examiner has identified a broad range of doses of administration, stating that "the claims [of the '117 application] read on any dose." Office Action, page 8, emphasis in original. Yet mere breadth of a claim alone cannot be the basis for a finding of obviousness. The purported range of the claim does not provide any information regarding what doses, blood concentration levels, plasma concentration levels, C_{max} in plasma levels, C_{max} in blood levels, AUC in plasma levels, or AUC in blood levels are preferred, necessary, or desired. Without some indication of blood and plasma levels or the like in the claims of the '117 application, it can not be obvious to one of skill in the art to select dosage amounts that would provide the presently claimed blood and plasma ranges.

Claims 52, 53, and Their Dependent Claims are Not Obvious In View of the '117 Application

Claims 52 and 53 recite elements not found in the claims of the '117 application and not addressed by the Examiner in the broadly stated ODP rejection. Independent claim 52, from which claim 63 depends, recites administering the compound of formula I to a subject, *and* exposing the subject to one or both of the compounds of formula II or III whereby one or more of the compounds of formula I, II or III provide a given range of combined C_{max} for one or more the

claimed compounds in the subject's plasma, or a given range of combined C_{max} for one or more of the claimed compounds the subject's blood. Independent claim 53 recites, exposing a subject having cancer to an amount of one or more compounds having a formula I, II, and/or III, sufficient to provide the claimed ranges of combined C_{max} in the subject's plasma or blood.

With regard to claim 52, and in addition to the reasons presented above with regard to claims 1, 9, and 36, the cited claims of the '117 application fail to teach or suggest either of the compounds of formula II or III (4-amino-5-fluoro-3-[6-(piperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and 4-amino-5-fluoro-3-[6-(4-methyl-4-oxido-piperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, respectively). In the cited claims of the '117 application, there simply is no teaching of the individual compounds, nor is there a teaching or suggestion of the exposure of the compounds of formula II and/or formula III to a subject. Without a teaching or suggestion of one or both of these compounds, Applicants submit that there can be no teaching or suggestion of exposing a subject to one or both of the compounds. Furthermore, without such a teaching or suggestion, one of ordinary skill in the art would not be cognizant of what to look for, or at what concentration to measure the provided blood and plasma ranges. There is no suggestion or teaching in the cited claims of the '117 application of each and every element of claim 52, as presented.

Independent claim 53, from which claims 54-58, and 64 depend, recites exposing the subject to a compound of a formula I, II, and/or III to provide a given range of combined C_{max} for one or more the claimed compounds in the subject's plasma or a given range of combined C_{max} for one or more of the claimed compounds the subject's blood. There is no recitation of the administration of any of such compounds in claim 53. In addition to the reasons presented above with regard to claims 1, 9, 36, and 52, the cited claims of the '117 application fail to teach the exposure of any of the claimed compounds to a subject having cancer.

Thus, not only do the claims of the '117 application fail to teach or suggest compounds of formula II or III and the combined C_{max} blood and/or plasma levels for those compounds, but the claims of the '117 application also fail to teach or suggest exposing a subject having cancer to

either of those compounds. The ODP rejection over the cited claims of the '117 application, therefore, fails on three fronts: first, the cited claims of the '117 application do not teach or suggest either compound; second, the cited claims of the '117 application do not teach or suggest exposing a subject to either compound; and third, the cited claims of the '117 application fail to teach or suggest the recited blood and plasma levels. Accordingly, the ODP rejection of claims 52 and 53 is improper.

Furthermore, Applicants direct the Examiner's attention to the fact that claim 62 depends from claim 49. Claim 49 has not been rejected under ODP in the present office action, and therefore "[i]f an independent claim is nonobvious..., then any claim depending therefrom is nonobvious." M.P.E.P. § 2143.03. Moreover, Applicants point out that there is absolutely no teaching or suggestion in the cited claims of the '117 application of the amount of the compound administered in a treatment cycle or that the amount is increased with each subsequent treatment cycle as recited in claim 49. As claim 62 depends from claim 49 and thereby contains all the elements of claim 49, there can be no teaching or suggestion of the subject matter of claim 62. Applicants respectfully request the Examiner withdraw this rejection with regard to claim 62.

In view of the above remarks regarding claims 1-7, 9-12, 14, 25-30, 36-38, and 52-64 in view of the claims of the '117 application, Applicants submit that the grounds for the ODP rejection are overcome and respectfully request that the Examiner remove the noted rejection.

B. U.S. 6,605,617

Applicants respectfully traverse the rejection of claims 1-38 and 49-64 on the ground of obviousness-type double patenting as allegedly being unpatentable over claim 30 of copending U.S. Patent No. 6,605,617 (the '617 patent). The present rejection is based on the assertion that "claim 30 of '617 is so broad so as to include administration of <u>any amount</u> of the claimed compounds to treat a VEGF mediated disease..." Office Action, page 11 (emphasis in original). Yet, as discussed above in Section IV.A. above, mere breadth of a cited claim alone is insufficient to obviate another claim. As the Examiner readily acknowledges, claim 30 of the

'617 patent does not teach or disclose any method of treatment directed to providing the claimed ranges of C_{max} or AUC, or the particular blood or plasma levels of the compounds of the present invention in a subject.

Claims 1, 9, 36 And Dependent Claims Are Not Obvious In View Of The '617 Patent.

As with the cited claims of the '117 application, claim 30 of the '617 patent is a general claim regarding methods of using compounds. Claim 30 recites, a "method of treating a patient in need of an inhibitor of vascular endothelial growth factor receptor tyrosine kinase, comprising administering an effective amount of the pharmaceutical formulation according to claim 29 to a patient in need thereof." (Claim 29 recites a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a compound of any of claims 1, 8, 15, or 22.) There is simply no suggestion or teaching of the currently claimed blood and/or plasma C_{max} or AUC levels, or blood and/or plasma concentrations. For this reason, and for all the reasons discussed, related to the ODP rejection over the cited claims of the '117 application, Applicants submit that the present ODP rejection of claims 1,9, and 36 and claims depending therefrom is improper.

Claim 49 and It's Dependent Claims are Not Obvious In View of Claim 30 of the '617 Patent

Likewise, claim 30 of the '617 patent cannot obviate claims 49-51 for the same reasons it cannot obviate claims 1, 9, and 36, claim 30. Claim 49, from which claims 50 and 51 depend, is directed to amounts of administration of the recited compound for a first treatment cycle and subsequent treatment cycles. Claim 50 is directed the amount administered in the treatment cycles, and claim 51 is directed to the length of the treatment cycles. By contrast, claim 30 of the '617 patent generally describes administration of a compound, but it does not provide any teaching or suggestion of the actual treatment cycle, the amounts administered in a treatment cycle, or if there is or is not a relationship between the amounts administered in one treatment cycle and any subsequent treatment cycles. Without some more specific teaching or suggestion regarding such matters, the ODP rejection of claims 49-51 over claim 30 of the '617 patent must fail.

Claims 52, 53, And Their Dependent Claims Are Not Obvious In View Of The '617 Patent.

Claims 52 and 53 recite elements not found in the claims of the '617 patent and not addressed by the Examiner in the broadly stated ODP rejection. Independent claim 52, from which claim 63 depends, recites administering the compound of formula I to a subject, *and* exposing the subject to one or both of the compounds of formula II or III whereby one or more of the compounds of formula I, II or III provide a given range of combined C_{max} for one or more the claimed compounds in the subject's plasma, or a given range of combined C_{max} for one or more of the claimed compounds the subject's blood. Independent claim 53 recites, exposing a subject having cancer to an amount of one or more compounds having a formula I, II, and/or III, sufficient to provide the claimed ranges of combined C_{max} in the subject's plasma or blood.

With regard to claim 52, and in addition to the reasons presented above with regard to claims 1, 9, and 36, claim 30 of the '617 patent also fails to teach or suggest either of the compounds of formula II or III (4-amino-5-fluoro-3-[6-(piperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and 4-amino-5-fluoro-3-[6-(4-methyl-4-oxido-piperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, respectively). In claim 30 of the '617 patent, there simply is no teaching of the individual compounds, nor is there a teaching or suggestion of the exposure of the compounds of formula II and/or formula III to a subject. Without a teaching or suggestion of one or both of these compounds, Applicants submit that there can be no teaching or suggestion of exposing a subject to one or both of the compounds. Furthermore, without such a teaching or suggestion, one of ordinary skill in the art would not be cognizant of what to look for, or at what concentration to measure the provided blood and plasma ranges. There is no suggestion or teaching in claim 30 of the '617 patent of each and every element of claim 52, as presented.

Independent claim 53, from which claims 54-58, and 64 depend, recites exposing the subject to a compound of a formula I, II, and/or III to provide a given range of combined C_{max} for one or more the claimed compounds in the subject's plasma or a given range of combined C_{max} for one or more of the claimed compounds the subject's blood. There is no recitation of the

administration of any of such compounds in claim 53. In addition to the reasons presented above with regard to claims 1, 9, 36, and 52, claim 30 of the '617 patent fails to teach the exposure of any of the claimed compounds to a subject having cancer.

Thus, not only does claim 30 of the '617 patent fail to teach or suggest compounds of formula II or III and the combined C_{max} blood and/or plasma levels for those compounds, but claim 30 of the '617 patent also fails to teach or suggest exposing a subject having cancer to either of those compounds. The ODP rejection over claim 30 of the '617 patent therefore, fails on three fronts: first, claim 30 of the '617 patent does not teach or suggest either compound; second, claim 30 of the '617 patent does not teach or suggest exposing a subject to either compound; and third, claim 30 of the '617 patent fails to teach or suggest the recited blood and plasma levels. As such, the ODP rejection of claims 52 and 53 is improper.

For the reasons above, Applicants respectfully submit that a *prima facie* case of obviousness has not been established for the obviousness-type double patenting rejection of claims 1-38 and 49-64 over claim 30 of the '617 patent. Applicants respectfully request that the Examiner reconsider and withdraw the noted rejection.

C. U.S.S.N. 10/886,950 and U.S.S.N. 11/342,257

Claims 1-7, 9-12, 14, 25-30, 36-38, and 52-64 stand provisionally rejected for obviousness-type double patenting over claims 13, 16 and 17 in copending U.S.S.N. 10/886,950 (the '950 application). Claims 1-14, 25-30, 36-38 and 52-64 stand provisionally rejected for obviousness-type double patenting over claims 1-5, 7-8, 10-17, 19-20 and 22 in copending U.S.S.N. 11/342,257 (the '257 application). As both the '950 and the '257 applications are still pending, the ODP rejections over the '950 and '257 applications remain provisional.

Applicants respectfully submit that the procedure set forth in § 804(I)(B)(1) of the M.P.E.P. is applicable to the present provisional double-patenting rejections. Section 804(I)(B)(1) of the M.P.E.P. states that

> [i]f a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw the rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Applicants point out that the instant application has an earlier filing date than either of the '950 or the '257 applications.

Because Applicants believe that, after entry of the above amendments and consideration of the remarks herein, no other rejections will remain in the present application, it is respectfully requested that the Examiner withdraw the provisional ODP rejection of claims 1-14, 25-30, 36-38 and 52-64 over the '950 application and the provisional ODP rejection of claims 1-14, 25-30, 36-38 and 52-64 over the '257 application, and allow this application to move forward to issuance. Applicants make no admission regarding the propriety of the double patenting rejection in this application over U.S.S.N. 10/886,950 and specifically reserve the right to challenge the propriety of this rejection, should it be maintained or issued in one or both of the latter-filed applications.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. If any issues remain to be resolved in view of this amendment and reply, the Examiner is requested to contact the undersigned by telephone to achieve a prompt disposition thereof.

Respectfully submitted,

Date March 2, 2007

By _____

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